DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Rese
1401 Rockville Pike
Rockville MD 20852-1448

December 20, 2002

By Certified Mail – Return Receipt Requested
And Facsimile Transmission

CBER – 03 - 005

Warning Letter

Roberta L. Luskin-Hawk, M.D.
AIDS Research Alliance-Chicago
Suite 108
2800 North Sheridan Road
Chicago, Illinois 60657

Dear Dr. Luskin-Hawk:

During the period of January 23, 2002 through February 15, 2002, and April 19, 2002 through May 3, 2002, Lisa Hayka and Mark Jimenez, investigators with the Food and Drug Administration (FDA), reviewed your conduct of the clinical study entitled "A Randomized, Open-Label, Study of ——————————————— on Viral Burden and CD4+ Cell Count in Patients with HIV-1 Infection and CD4÷ Cell Counts ————————This inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

A Form FDA 483, List of Observations, was issued to and discussed with you at the conclusion of the inspection. We have reviewed your written response letter dated July 30, 2002 to the Form FDA 483. In your response letter you acknowledge that there were deficiencies in the conduct of the above listed study, and agree in principle to the correctness of each of the noted observations. You further state that you are committed to improving compliance with FDA regulations.

Based upon the inspectional findings described in the Form FDA 483, and our subsequent review of documents collected during the inspection, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312, which are available at http://www.access.gpo.gov/nara/cfr/index.html. The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to fulfill the general responsibilities of investigators. [21 CFR § 312.60 and 21 CFR § Part 50].**

   An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, protocol, and all applicable regulations for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of drugs under clinical investigation.

Our investigation documented that you did not fulfill your obligations as a clinical investigator in that you failed to follow the investigational plan and failed to adequately protect the rights, safety, and welfare of subjects under your care. Specific examples of these violations are described below.

A. You failed to conduct an investigation according to the signed investigational plan and protocol. [21 CFR § 312.60].

i. The protocol required subjects to have a baseline history and clinical evaluation not more than 30 days prior to subject randomization in order to document that all eligibility criteria was met prior to entry into the study. There are no records to document that this was done for the following subjects:

- [redacted] clinical evaluation done on 10/30/98, randomized on 12/3/98.
- [redacted] clinical evaluation on 1/19/99, randomized on 2/22/99.
- Subject [redacted] clinical evaluation on 1/20/99, randomized on 3/4/99.
- Subject [redacted] clinical evaluation on 12/23/98, randomized on 3/15/99.

ii. The protocol required a clinical evaluation to be done prior to Cycles 2 and 3. The case histories fail to document that the following subjects had the required evaluation:

- Subject [redacted], Cycles 2 and 3
- Subject [redacted] Cycles 2 and 3
- Subject [redacted] Cycles 2 and 3
- Subject [redacted] Cycle 3
- Subject [redacted], Cycle 2
- Subject [redacted], Cycle 2

iii. The protocol required that subjects receiving [redacted] should be closely monitored and phone contact should occur daily during cycles when patients self-administered the investigational drug. There is no record that the following subjects were contacted during the initial cycles of [redacted] as required:

- Subject [redacted]
- Subject [redacted]
- Subject [redacted]

iv. The protocol required that all adverse events were to be graded and evaluated by site medical personnel. The adverse events self-reported by subject [redacted] during Cycles 1 and 2 are not documented on the Dose Tracking Form, or on any other record available during the inspection, as being graded or evaluated.

v. The protocol required that the reason for dosage reductions be reported to the Statistical Center. The dosage for subject [redacted] was decreased from ——— to ———after Cycle 1 due to several reported adverse events. There are no records to document that the reason for the dosage reduction was reported to the Statistical Center.

vi. The protocol required a physical examination to be performed for all subjects enrolled in the study at 4, 8 and 12-months. Subject [redacted] had an initial physical on 10/30/98. The next documented clinical evaluation was done on 8/5/99. There are no records that document the protocol required 4-month physical examination was performed.

vii. The protocol required HIV bDNA assays to be done monthly for the first 12 months. There are no records to document that this was done for the following subjects and time points.

- Subject [redacted]; Months 2, 8, and 9
- Subject [redacted] Months 5 and 6

viii. The protocol required that CD4 cell counts be drawn on day 29 (±5 days) for each Cycle. There are no records to document that this was done for the following subjects and time points.

- Subject [redacted]; Cycle 2 and 3
- Subject [redacted] Cycle 3
- Subject [redacted]; Cycle 1 and 2

ix. The protocol required ——to be reconstituted under aseptic conditions (i.e., under a hood) if drug was to be provided to subjects in pre-loaded syringes. The pharmacy responsible for dispensing reconstituted —— did not have a hood until approximately 6/99. Pharmacy Accountability Records document that subject [redacted] was dispensed a total of 7 pre-loaded syringes of reconstituted——on 12/2/98 and 3/19/99.

x. The protocol required that the study drug be dispensed only upon the written order of the investigator. The Investigational Agent Accountability Record documents that subject [redacted] was dispensed—— on 11/20/98, but the pharmacy did not receive the prescription until 11/24/98.

Your response letter acknowledges the above listed deviations i through x, and your proposed corrective actions appear to be adequate if implemented and followed.

xi. The protocol stated that concomitant administration of glucocorticoids had been shown to———————————— and should be avoided. The case histories document that the following subjects were prescribed and administered Prednisone® during the study.

- Subject [redacted]
- Subject [redacted]
- Subject [redacted]

In your written explanation you stated that the term "should" is not an absolute prohibition. However, we remind you that since the primary objective of this study was to show the efficacy of ——, any data derived from a study subject administered glucocorticoids may be impacted by those drugs.

B. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].

An investigator must obtain consent from prospective subjects under circumstances that provide the subject with a sufficient opportunity to consider whether or not to participate. All reasonably foreseeable risks or discomforts to the subject, and any new significant findings that may relate to a subjects willingness to participate must be disclosed. The consent form for this study did not include all reasonably foreseeable risks and did not disclose significant new findings as described below.

A safety report dated 11/9/99 reported on a second case of optic neuropathy/retrobulbar neuritis. The sponsor felt this adverse reaction was related to the subcutaneous administration of—— The sponsor recommended that the potential risk of optic neuritis be included in the informed consent document. The sponsor provided specific phraseology and stated that other investigational sites had already revised their informed consent documents to include the potential risk of optic neuritis.

However, you did not revise the consent form to include the possibility of severe neurological side effects. You therefore failed to ensure the rights, safety, and welfare of subjects by withholding significant new findings that may relate to a subject's willingness to participate in the study.

Your written response and proposed corrective action appears adequate if implemented and followed..

2. You failed to prepare and maintain adequate and accurate case histories. [21 CFR § 312.62 (b)].

An investigator is required to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation for each subject. The following are examples of incomplete or inaccurate case histories.

i. A medical record dated 5/24/00 reports that the subject [redacted] was seen for the start of —— Cycle 5 and the first injection was given on that date. However, there is no——Dosing Cycle Case Report Form (CRF) for Cycle 5.

ii. There are no records in the case history for subject [redacted] to document that monthly viral load assays for Visit Month 1 and 2 were done.

iii. A nursing note dated 3/12/99 (——Cycle 1, Day 5) reports the subject [redacted] had flushing of the face and hands, a grade II reaction. A nursing note date 5/3/99 (Cycle 2) states the subject had severe chills, a grade II reaction. An entry dated 9/23/99 states that all symptoms related to the administration of ——were grade I. There is no documented explanation for the change in grading of the reported reactions from grade II to I.

iv. Clinical investigator progress notes of 10/30/98, 11/9/98, 1/11/99, 8/5/99, and 8/18/99 for subject [redacted] contained changes that were not initialed or dated, and were illegible.

Your response letter acknowledges these deviations, and your proposed corrective actions appear to be adequate if implemented and followed.

3. Failure to maintain adequate records for disposition of the test article. [21 CFR 312.62(a)].

An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, and to return all unused supplies of the drug to the sponsor. The following is an example of inadequate recordkeeping and disposition of the investigational drug product that was under your control.

Each subject who self-administered——from reconstituted vials was to return all empty vials at the end of each cycle. There were approximately 33 subjects in the study; each was dispensed 10 vials of ——per cycle. Pharmacy records document that for Lot number ———— over 300 vials were received and dispensed. However, only 30 empty vials of Lot ————were documented as being returned and destroyed.

Your response letter acknowledges this deviation, and your proposed corrective action appears to be adequate if implemented and followed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study. It is your responsibility as the principal investigator to ensure adherence to the signed investigational statement, the investigational plan and the protocol, as well as to each requirement of the law and applicable regulations, and to protect the rights, safety, and welfare of subjects under your care.

In your written response letter dated July 30, 2002, to the Form FDA 483, List of Observations, you described corrective actions to each of the cited deviations. These included the re-education of key personnel, implementation of new policies, and the addition of a new Quality Assurance and Education Manager, all of which are designed to prevent reoccurrence of the noted violations in future studies.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, and/or the commission of other violations may result in the initiation of enforcement action(s) without further notice. These actions could include FDA seeking injunctive relief or the initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

Please advise us within 15 days of receipt of this letter of your estimated timetable for completion of the planned corrective actions. Your response should be addressed to:

Robert L. Wesley
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 457S
Rockville, MD 20852-1488
Telephone:(301) 827-1948

Sincerely,

/s/

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: